Poisoning the Spindle: Serendipity and Discovery of the Anti-Tumor Properties of the Vinca Alkaloids

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Abstract. In 1995, Canadian scientists Robert Noble and Charles Beer were inducted into the Canadian Medical Hall of Fame for their 1950s “discovery” of Vinblastine. Their “chance” finding of an anticancer drug in the leaves of the periwinkle plant (Vinca rosea, Linn.), is used to explore the historical issue of discovery, accidental discovery, and priority. The elements of the discovery are reconstructed through the oral testimony of key players and their published and unpublished records. Several “unsung heroes” played key roles in this project and reasons for their relative invisibility will be presented. Special attention is paid to the relationship between the small Canadian academic group working at UWO and the large pharmaceutical company (Eli Lilly) engaged in similar research at the same time.

Résumé. En 1995, les scientifiques canadiens Robert Noble et Charles Beer ont été accueillis dans le Canadian Medical Hall of Fame en raison de leur découverte, au cours des années 1950, de la Vinblastine. La découverte, qu’ils firent par «chance» d’un médicament anti-cancéreux dans les feuilles de la plante de la pervenche (Vinca rosea, Linn.) est utilisée ici pour étudier les questions historiques de la découverte, de la découverte accidentelle, et de la priorité. Les éléments de la découverte sont reconstruits à partir du témoignage oral des acteurs principaux et à partir des récits et documents publiés ou non publiés qu’ils en ont laissés. Plusieurs héros non-célèbres ont joué un rôle clé dans ce projet et l’on expose les raisons qui expliquent leur relative invisibilité. On accorde une attention particulière aux rapports qui existaient entre le petit groupe académique canadien qui travaillait à l’Université de Western Ontario et la grande compagnie pharmaceutique (Eli Lilly) qui poursuivait, au même moment, des recherches similaires.

In 1997, distinguished researchers Charles Beer (b. 1915) and the late Robert Noble (1910-1990) were inducted into the Canadian Medical Hall of Fame.
Hall of Fame for their "chance" discovery of the first cancer remedy in periwinkle. Noble was recognized for "his discovery of "vinblastine"" (VLB) a drug derived from the Madagascar periwinkle plant (Vinca rosea, now called Catharanthus rosea); Beer, "for isolating" it in 1958. The Hall of Fame tells us that the first clinical trials were conducted at Princess Margaret Hospital in 1959. Among other questions, this paper will ask: did Canadian scientists really discover the cancer remedy in periwinkle? Was their find, as they said, owing to "chance"? And if so, how exactly did chance lead them to study a plant that does not grow in this country?

Forty years later, Vinca derivatives continue to hold pride of place in combination chemotherapy, making them among the earliest and most durable of effective anti-cancer agents. They were the first in a new class of drugs, now called stathmokinetic agents, or spindle poisons, which are said to "work" by attacking the microtubule spindle that pulls the chromosomes apart during mitosis, or cell division. Not only do they kill malignant cells, they bring dividing cells into synchrony thereby increasing their susceptibility to subsequent treatments with other drugs. The class includes the podophyllotoxins, derived from the May apple plant, and taxol, derived from the Pacific yew tree.

Hematologists the world over have treated countless tumors, especially leukemias and lymphomas, with Vinca derivatives. The drugs are also applied to autoimmune conditions, sometimes with imaginative methods. For example, the drug’s property of binding to platelets inspired the "washing" of donor platelets in Vinblastine (VLB) to create the "poison-platelet" cocktail for treatment of immune thrombocytopenia. A VLB-coated platelet would kill any hapless reticuloendothelial cell that dared to ingest it.

Canadian hematologists know that these drugs were first isolated in our country and they are familiar with the charming story of the "discovery." From a historical perspective, however, one of the most intriguing aspects of this tale is that the original scientific declaration of the discovery contained what the authors themselves called a "somewhat unorthodox" account that assigned a starring role to chance.

Chance is a contested issue in the historical, sociological, and philosophical literature pertaining to discovery. Some contend that it has no role in discoveries; others think that it is crucial. Many would suggest that discovery itself is contentious—a process honed through retrospect rather than a momentary flash of insight. Long intrigued by the Vinca story and having just crawled out from under a lengthy project on another "big discovery" (auscultation), I used the excuse of this conference to examine the Vinca story a little further, hoping to bring it into the context of the now burgeoning but highly diverging histories on scientific discovery. My sources include the publications of periwinkle re-
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searchers in Canada and the USA, transcripts of Charles Roland’s interviews with several key figures, and my own contacts with these and other players. My paper is divided in four. First I will summarize the historical literature on chance and discovery; then I will briefly recount the master narrative as told by Robert Noble; then I will expand on that narrative in four ways using variations in subsequent retellings and other evidence. The results show that many different things were discovered in (and around) the periwinkle plant by many different people and over an extended period of time. Finally I will bring the Vinca tale back to the historiographic problem of chance in discovery, trying to situate the former in the latter and the latter in the former.

HISTORY OF DISCOVERY 101: OBSERVATION, CHANCE, PRIORITY, AND GREAT MEN

When scientific discovery is mentioned, the names of great men (and maybe a few women) spring to mind: Galileo, Kepler, Leeuwenhoek, Semmelweis, Einstein, Curie, Banting, Fleming. This natural reflex creates a problem for historians who study discovery. In an historical climate that is hostile to biography and suspicious of great men, priority easily dissolves into a reductionist soup of context and jealous precursors. Individual observation and rare flashes of insight—the famous Archimedean “Eureka!”—are mistrusted for being vested with retrospective value. A number of distinguished historians, A. C. Crombie, René Taton, and my own thesis advisor Mirko Grmek among them, cautioned against succumbing to the historiographic “myths” of discovery that tend to frame and enhance retrospective accounts.4 In his long list of cautions, Grmek included the suspect-reliability of existing historical records about any discovery and the tendency to describe events in structural terms. He argued that accounts of discovery are necessarily (though innocently) constructed post hoc. Only with other evidence, such as laboratory notebooks or clinical records, can we actually attempt to reconstruct discoveries as functional processes, in physiological terms, rather than in anatomical or structural terms that tend to feature the accumulation of discrete nuggets of understanding. Yet, even with access to these privileged sources, objectivity can continue to be elusive. Possessing only the subset of accounts that were actually recorded and then managed to survive, we must view both the printed and manuscript records as merely partial testimony.5 We can diligently try to gather additional papers and oral testimony from survivors and descendants, but all evidence is a product of who does the recording, who does the preservation, and who does the seeking. Historical objectivity is difficult, and it may well be a pretence.6

Sociologists of science agree with historians that priority is a complex tangle and that individual flashes of insight are less brilliant than they
may at first seem. Inspired by a 1922 article published in a political science periodical, R. K. Merton argued famously (andconvincingly to my mind) that most discoveries are "multiples,"or the result of simultaneous, independent work; singletons are the exceptions.\(^7\) He assembled more than 200 examples to make his case. With Merton, sociologists have shown how personal and national pride, perceived "races," priority disputes, and other forms of competition are a product of the norms of the "reward system" of science that demands originality and can act as a stimulus to scientific activity—even in retrospect. But they can also lead to what Merton called "deviant" behavior such as fraud and plagiarism, or (more often) accusations of both.\(^8\)

In a pragmatic response to Merton's views, Augustine Brannigan argues that discoveries are singletons after all, especially because scientists see them that way. Precursors aside, the discovery is not only the observation, but also collective agreement with that observation and justification of the claim to priority. He suggests that the unsung precursors should not matter or count; recognition for a discovery rightly belongs to the person who succeeds in convincing others, usually through the printed record.\(^9\) In other words, discoveries are not events; rather they are constructs that have won acceptance.

The creative component of discovery has been likened to the aesthetic impulse and judged to be "irrational." Consequently, philosophers of science tended to dwell on the "logic" of scientific judgment and method, but they avoided addressing discovery because of its supposed inherent lack of logic. Even those who purported to write about discovery, including Karl Popper and Thomas S. Kuhn, have been accused of sliding around the central issue of discovery in favor of its preconditions and its consequences.\(^10\) Recognizing these difficulties, scholars have recently reconstructed the problem by altering the focus on "discovery" to a focus on "innovation," a term that is both lesser and greater than its precursor.\(^11\)

Examples of discoveries that have been attributed to chance or accident abound.\(^12\) But chance has suffered in the scholarly literature of the late 20th century, together with priority, creativity, and great men. After a decade or more of trying to minimize the role of chance, sociologists now tend to ignore it.\(^13\) Nevertheless, some scientists of the 1960s and 1970s were so impressed with the connection that they fretted over how to generate policies and funding conditions that could somehow foster chance.\(^14\) Even when the scientists involved \textit{wish} to give chance centre stage, historians and sociologists are sceptical. They contend that chance may help to juxtapose two events, but something else is needed to take advantage of the accident. To win the lottery you need a lucky ticket—the Pastorian "preparation of the mind."\(^15\) The observation of
Alexander Fleming is often trotted out as a case in point: for decades, scientists had reported having their plates spoiled by mould; the difference between Fleming and his precursors was that he had long been conscious of the search for magic bullets. In other words, to discover B while looking for A, you must also know that B is being sought.

Some writers attempt to distinguish between chance and its near synonym serendipity; they refer to Horace Walpole’s original definition, featured in the Oxford English dictionary, that serendipity was “accident combined with sagacity.” The choice of this “serendipity” over “chance” allows for a return of great men through the “sagacity” of individual imagination. According to some, however, this definition of serendipity diminishes chance by replacing it with “genius” or a “prepared mind.”

Careful examination of any seemingly discrete achievement usually uncovers a labyrinth of precursors, both conceptual and personal. These are what Brannigan referred to as the “naturalistic—historical or psychological—preconditions,” which require further “attributational” preconditions to turn an observation into a discovery. Identification of precursors tends to reduce the breadth of the heuristic quantum leap of a discovery, as judged through a distance of time and familiarity. If these precursors are taken as evidence of multiple discoveries, the role of chance melts—if not into necessity—then, at least, into cultural inevitability.

Recently, one philosopher bravely tried to create an “evolutionary epistemology” to bring back “serendipity” into an equation of discovery. Like the scientist-observers of two decades ago who worried about the stifling narrowness of funding arrangements, he goes so far as to advocate “rules” for fostering opportunities for chance in research. But he does so against a tide of opinion.

In short, scholars do not leave room for chance in discovery; some even suggest that discoveries do not exist naturally without attributational construction. One gap in this literature can be discerned. A number of histories of the pharmaceutical industry have been written, but few address questions of its relationship to academe or its impact on the process of scientific discovery. It is clear that the change to increased industrial support has been compatible with continued discovery; several scientists have conducted Nobel-award-winning work while in the employ of major pharmaceutical firms. It is not clear, however, how this important shift in research support has altered the nature of the questions, methods, and especially the justifications of discoveries. The Vinca research could eventually be seen not only as a case study of chance in discovery, but as an example of this interface between academic science and industry in a larger history that has yet to be written.
Son of a Toronto doctor, Robert Noble was just 11 years old when his older brother, medical student Clark, worked close to the Toronto team that would win the Nobel prize for insulin. He grew up with and absorbed a partisan version of the tale about Frederick Banting and J. J. R. Macleod. He remembered "quite distinctly" that his brother Clark and Charles Best "were great friends... they tossed a coin to see who would go with [whom]... my brother won the toss and he'd never heard of Banting so he went with Macleod." Friction within the team led Banting to share his half of the Nobel prize with Best, and Macleod to share his with the biochemist, J. B. Collip. As a result, the coin toss can be taken as evidence of how chance caused a Noble to narrowly miss a Nobel. Indeed, the younger Noble later admitted, "the family was sort of bound up by it." Discovery, priority, fame, fortune, jealousy, betrayal, and chance—that controversial "coin toss"—were themes that haunted the people around him. It is scarcely surprising that the same themes recurred in his own life.

As a medical student himself, Robert Noble became a protégé of Macleod who was a friend of his father as well as his brother. Noble studied medicine in both Aberdeen and Toronto, completing his M.D. at the University of Toronto in 1934. Wanting to pursue a career in cancer research, he was nudged by Macleod into endocrinology instead. After a five-year association with the Courtauld Institute, he earned a doctorate from the University of London in 1937. He returned to Canada to take up a position at McGill University with Collip. During the war, Noble and Collip studied motion sickness and ways to minimize it. They also devised a rotating drum to create the conditions of traumatic shock in experimental animals. In 1947, when Collip moved to UWO, Noble followed to become Professor of Medical Research and Associate Director of Collip's new laboratory. The isolation of VLB was that laboratory's biggest discovery.

In March 1958, speaking on behalf of his small team, Noble read the original vinca paper with its master narrative at a cancer research symposium at the New York Academy of Science. He said the "chain of events" began in 1949 when the Collip lab—ever devoted to endocrinology—was investigating the presence of hormone activity in "various plant extracts to which historical hearsay had ascribed empirical uses by primitive peoples." He continued,

The disease of cancer was certainly far from our minds when we learned of a tea made from the leaves of a West Indian shrub that was supposedly useful in the control of diabetes mellitus. C. D. Johnston of Black River Jamaica... had been curious about the benefits of a tea made from... periwinkle... and he forwarded a supply of the material to us.
Researchers everywhere were keen to find a source of oral hypoglycemic agents that would eliminate the needle injections required by insulin. But oral administration of periwinkle extracts in rats had no effect on blood sugar or glucagon levels. Noble sent pediatrician John C. Rathbun and endocrinologist Hugh A. McAlpine to visit Johnston in Jamaica to find out more about the preparation of the tea. Much later the investigators learned that the antidiabetic potential of oral periwinkle had already been investigated and refuted by Australian researchers in the late 1920s.28

Trying to improve on their own results, Noble's team decided to inject the water extracts of periwinkle into the rats. This time, he said, the animals were "obviously affected but in an unexpected manner": they all died. Autopsy revealed multiple abscesses. The team noted that the offending bacteria (Pseudomonas) were the same as those "isolated in rats ... receiving large doses of cortisone." Noble continued: "Apparently some natural barrier to infection was being depressed by both types of treatment. Further studies readily localized the action of the V[inca] rosea extracts—a rapidly falling white blood count, granulocytopenia, and profoundly depressed bone marrow."29

Noble's lab worked "spasmodically" on the problem, he said, and "an intensive study was not started until 1955."30 He went on to explain the elegant biochemical work accomplished to isolate the active substance by extraction and chromatography, using the white blood count as an assay. Preliminary studies of the activity of the unpurified extracts were published in 1955 and 1957.31 A photograph of the crystalline product accompanied the 1958 paper. He concluded with a report of the effects on blood and bone marrow of healthy rats given the purified substance. Due to a lack of materials, only "limited investigations for carcinostatic [anti-cancer] activity" had been made in vitro on a transplantable mammary adenocarcinoma of the mouse and a transplantable rat sarcoma.32

In framing his remarks, Noble acknowledged the "awe" that "the cancer worker in the smaller institution" must feel in viewing the "vast chemotherapeutic screening projects" of industry; however, he continued, "perhaps the role of chance observation is neglected in his consideration of ways of searching for new agents."33

MASTER NARRATIVE REVISITED: #1 WHO? WHAT? WHEN?

Noble had occasion to amplify on his story because he was asked to retell it many times in person and in print. It was picked up (and distorted) by the media, including Reader's Digest,34 and repackaged in various guises—the "small-local-hero" version, or the "new-cure-for-cancer-
cer' version or the "amazing-but-true!" version—most of which, as he later told Charles Roland, made the team quite uncomfortable.35

In his Terry Fox lecture of 1984, Noble provided more context and added to the story.36 He attributed the observation of the drop in white cell counts to Dr. Vernon Colpitts.37 Noble also revealed that C. D. Johnston of Black River Jamaica was a surgeon who had graduated from McGill University in Montreal. Johnston’s 1914 graduation photograph shows that the Jamaican-born graduate was black (Figure 1).38 Noble made this interesting observation to Charles Roland, but it was never mentioned in print, although it must have been known to the Noble team following the Jamaican journey of McAlpine and Rathbun.

Figure 1

Dr. C. D. Johnston and Julia Seager Johnston. Family photographs provided by their granddaughter, Sandy Macintosh of Kingston, Jamaica.

Johnston’s connection to Canadian research demands some explanation. Born in 1885, Johnston was already officially retired at the time of the Vinca research. He had been given the Order of the British Empire in 1947 for his more than 30 years of service to the Black River community. His first wife Julia Seager (d. 1958) had met Johnston when they were both in nursing school at Battle Creek, Michigan. They embarked together on medical studies, which he alone completed.39 Periwinkle was only one of his many interests. He died on 15 October 1968.
After the Canadians noticed the effect on white cells, a sufficient supply of leaves for further studies became an issue. Dr. Johnston organized troops of boy scouts to collect leaves in the forest. His granddaughter recalls that it was Mrs. Johnston, who presided over the collection of leaves, drying them on her verandah and packaging them for shipping to Ontario.40

Another person entered the Vinca story. Almost always referred to by Noble as “a Miss Farquharson,” she was the first to bring the supposedly anti-diabetic leaves from Dr. Johnston in Jamaica to Robert Noble’s brother, Clark.41 Interested still in insulin, but no longer in research, Clark gave the leaves to his brother. Unfortunately, Clark Noble’s children have no records pertaining to these events, although they are familiar with the story.42 And so far, Miss Farquharson has eluded identification. She has been variously described as “a patient of Clark Noble,” a Jamaican maid, an employer of a Jamaican maid, an employee of the Banting Institute, and a relative of Toronto Professor of Medicine Dr. Ray Farquharson (the latter connection, fervently denied by Ray’s hematologist daughter, Helen [“Nell”] Farquharson). I’m still looking for Miss Farquharson, but I fear that she will remain shrouded in mystery like so many other obscure women of medicine’s past, such as Jenner’s dairymaid, Mrs. Hutton of digitalis fame, and the “ignorant Scots woman” who brought ergot to the attention of James Stearns.

Supply continued to be a serious problem. The quantity of leaves needed to make the drug was often described as an ounce of drug from 15 tons of leaves.43 Noble eventually entered into a supply agreement with the large family-owned Swain greenhouses, still located in West Lorne, Ontario.44

In these later versions of his story, Noble reported that when confronted with the abscesses, Collip abandoned hope that the leaves contained insulin and began wondering if Vinca might be a source of cortisone.45 They had been following the work of Hans Selye, their former colleague in Montreal. In 1951, Selye published on the effect of adrenocortoid hormones; toxic doses in the rat produced multiple abscesses with *Pseudomonas* bacteria.46

In all versions of his story, Noble acknowledged that the extraction, isolation, and purification of vinblastine was the achievement of his chemist, Charles T. Beer. Born in England, Beer first came to Canada in 1954 as a British Empire Cancer Campaign Fellow, having spent three years at New York’s Sloan Kettering Institute for cancer research. Beer’s work in London, Ontario, was interrupted by a year at McGill in 1955-56. When he returned, he was able to isolate, purify, and crystallize the active agent, which he and Noble named “vincaleukoblastine” (later shortened to vinblastine)—for its derivation from periwinkle
(Vinca) and its effects on white cells. Beer's method consisted of making extracts with various solvents and then separating the components using fractional precipitations, paper and column chromatography. He injected the separated components into rats and used the fall in the white cell count as an "assay"—the indicator of activity. Beer described the chemical process to Charles Roland:

"This was old-time organic chemistry... you have a very crude mixture, and we had a little brown gummy mess really; you try and dissolve it in an organic solvent... Then you allow it to cool slowly and the hope is that the substance you're interested in will come out crystalline but leave the impurities behind... then you filter, you pour off... the brown gummy liquid on the top and you have this little pad, tiny pad of white crystals..."

I didn't have enough..., and so I was doing it on a microscope, under a microscope slide. Running little amounts of solvent in under the coverslip and then watching the edge of the coverslip, where the liquid was oozing out, and it's evaporating, and if you see a crystal there, then you think you are beginning to see the fox, even if you haven't got it.

You have a tremendous range of solvents. Benzenes, alcohols, acetone, petroleum, ether. Sometimes you use mixtures... These compounds we already knew were in the class known as alkaloids, and this gave us a little bit of an extra handle on it... Just a matter of trial and error. Mostly error for several months...

It took about 5,000 attempts. About 250 columns were tried... You would get 100 to 150 fractions off each column, and the assay of these [using white cell counts in rats injected with the extracted fractions]... was of course quite a big job... demanding in time. Since most of the fractions weren't active anyway. We designed the column... on the basis of the results we obtained.

One night I'd had supper in the restaurant at the University of Western Ontario campus, somewhat depressed, and talking to a colleague and he said, "How's the crystallization going?" I was on the point of going home, but this remark goaded me or stimulated me to go back and have one more shot in the lab. I was looking down the microscope field and I saw like a tiny dot of light in the field, and suddenly a long shining spear-like object radiated from this little dot. Eventually the whole field was filled with a mesh of little crystals and that was it!

Beer was right that the work, which he described so eloquently, placed the research in enticing but established territory. Plant alkaloids had first been identified and isolated in the second decade of the nineteenth century, with work on morphine, ipecac, and quinine; indeed, these achievements produced a conceptual shift in chemistry. In the first half of the twentieth century, much excitement and many Nobel prizes—for hormones, vitamins, and antibiotics—had emerged from the tradition of identifying activity, isolating the agents, purifying, and eventually synthesizing the products.

Noble later revealed that the original 1958 paper had been submitted to the cancer symposium at the last minute when he was approached by
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the organizer, Dr. Chester Stock. The meeting ran late. When the team from Canada rose to present their findings, it was already midnight; the audience was reduced to a handful of willing listeners, mostly members of a team from the Eli Lilly drug company, led by the director of research, Irving S. Johnson. As Noble told it, the title of the paper had "caught Johnson's eye." Johnson himself told me that he, too, was speaking at the meeting; having seen the abstract circulated with the program, he had telephoned Noble in advance to ensure their meeting. Beer described the phone call as "frantic"; Johnson was more sanguine.

According to Irving Johnson, the Eli Lilly company had been engaged in "a huge screening program" of the awe-inspiring type alluded to by Noble. It was "conducted by the NCI under the auspices of... the Cancer Chemotherapy National Service Center (publishers of Cancer Chemotherapy Reports)." Lilly had been supporting Johnson and his team in a search for anti-cancer agents by testing up to 5,000 materials a year, including a wide range of plant extracts, against various animal tumors. They had heard reports from the Philippines about periwinkle and diabetes; however, the plant screening project was not specifically targeting diabetes, although Noble, Beer, and others often said that it was, an assumption based on Lilly's connection to insulin production in the past.

The Eli Lilly company had originally wanted its team to use just one line of tumor cells in screening tests (L-1210 mouse leukemia), but Johnson knew that drugs might be effective for only some tumors. He had argued for the use of others, including the P-1534 mouse leukemia. Years later, he expressed justified satisfaction that his views had prevailed: Vinca had no effect on the first cell line, but it was effective against the additional cell line. By the time Noble's team went to the New York meeting, Eli Lilly company already had documented the anti-tumor effect of the drug in mice. But, Johnson admitted, they had yet to publish those results. In conversation with me, he pointed out that 60 different alkaloids were eventually isolated from the plant. He readily acknowledged that Charles T. Beer "certainly did" hold priority for devising a method for isolating the alkaloid VLB.

During 1958, Lilly adopted Beer's method and quickly began trials on animal tumors with VLB (called Lilly 29060-LE). Johnson reported the anti-tumor effects at two meetings in the following year. In both abstracts, his team took the opportunity to retrospectively stake their own claim to priority by situating their observation of the anti-tumor activity in December 1957—four months before the meeting in New York City. Until late 1959, Lilly labs acknowledged the provision of "authentic" VLB from Noble's team. Lilly's isolation chemist, Gordon H. Svoboda,
began working on another isolate, Leurosine, which he had named for his father, Leo. Some reports imply that he had isolated the chemical before Beer had isolated VLB; however, published reports of Leurosine did not appear until late 1958.

A "controversy" between Beer and Svoboda ensued. Tension can be traced through the footnotes of their publications. Svoboda's isolate had weaker activity over a narrower range of tumor types, but he doggedly kept up work on his father's namesake, always emphasizing Lilly's priority and the drug's effectiveness. Leurosine was found to have an effect on animal tumors similar to that of VLB, and an effect on human tumors transplanted into animals. It was brought to human trials, Johnson told me, but never licensed commercially. Noble thought that Svoboda's Leurosine appeared to have activity because it was contaminated with VLB. But Beer told Charles Roland that spectrophotometry of VLB and Leurosine initially showed superimposable spectra—despite differences in the two substances. Beer said "they had got out something which was essentially inactive. Very very negligible activity. The reason it was overlooked" was owing to methods "used for measuring the spectra [that] used a mineral oil mull, in preparing the sample, and that makes an opaque area in the scan... It took quite some months before it was pinned down as to what was going on."

Once the Leurosine-VLB situation was sorted out, the Canadian lab had "from that point on, quite a close, very happy arrangement with Eli Lilly." Noble's team visited the Lilly lab in Indianapolis and the Lilly team came to Western. Beer described the differences to Dr. Roland:

> Our columns that we used for separating things were about half an inch in diameter and perhaps fifteen inches long. Tiny things. The liquid would be drained, go through quite slowly, and come out in a drip, and it dripped quite slowly... When I went down to the Eli Lilly company, I would see a pipe about ten inches or a foot in diameter and thirty feet long, going up through the building, and solvent going in at the top from a barrel and running out like water from a faucet at the bottom, so they had—and they were processing, I am sure, literally tons of the plant.

The Canadians tried to maintain their own supply of periwinkle, but it soon became obvious to all concerned that they "could not compete" with the resources available at Lilly. The earliest trials conducted in Canada indicate that the VLB was "prepared in the Collip Laboratory... from material kindly supplied by the Eli Lilly Co."

Beer and Noble had funding from the Medical Research Council (MRC) and the National Cancer Institute of Canada (NCIC). These bodies required that a patent be sought for all discoveries made in research that it funded. Beer's method for isolating vincaleukoblastine was patented in the names of Noble, Cutts, and Beer in late 1962.
pany helped in drawing up the patent and were the original leaseholders. According to Noble, the patent was offered to the MRC and the NCI, but, Noble claimed, they “did not wish to hold it.” It was taken over by President Edward Hall of UWO to which Noble’s team sold their interests for a dollar. But Noble and Beer left for Vancouver in 1960. Noble said the funds “helped,” but he complained to Charles Roland that the arrangements might have provided “a lot more research funds if we’d stayed at Western where they created a fund with royalties... [which] continued for 17 years.” Yet Harold Warwick, the former Dean of Medicine at UWO, remembers writing cheques to Noble on the proceeds of the patent, and he told Charles Roland that if Noble “didn’t get the money, he’d always write to [me] and say, ‘Where is it?’”

The question of who discovered the anti-cancer properties of the Vinca alkaloids seems less clear now than at the outset of this paper. Two teams were involved in the process researching the issue from two different angles, although they relied on the same well-established methods in biochemistry. Behind the teams were a number of lesser known (and less knowable) individuals, in Jamaica, Australia, and the Philippines, who had investigated the healing properties of these plants. When the discovery was made is even more difficult to determine. In fact, isolation of the drug notwithstanding, “discovery” of its anti-cancer properties still required proof in real patients.

MASTER NARRATIVE REVISITED: #2 CLINICAL TESTING

Until late 1958, only rabbits, rats, mice, hamsters, and cells in petrie dishes had been treated with the promising new drug. Using VLB on humans was the next step. From this distance, it appears that there was a race—even a little stampede—to be the first to do so, although the people whom I interviewed hesitated to call it that (see Table 1).

Noble seems to have hoped that the clinical testing would be done in Canada. In his lectures, he credited the first human trials to Dr. Harold Warwick at the Princess Margaret Hospital and to Dr. Mac Whitelaw of Vancouver, each of whom published a large series with impressive results in Hodgkin’s disease and lymphosarcoma. Almost as an afterthought, Noble mentioned Dr. M. E. Hodes of Indianapolis who “also observed beneficial effects on cancer patients” using VLB supplied by Lilly company. But in an interview with Dr. Roland, Noble acknowledged Hodes’ priority. Warwick may hold the honor for Canada, at least, and his trial was without question the largest.

Harold Warwick was newly returned to Canada from Royal Cancer Hospital and Brompton Hospital in London, UK. There he had directed a clinical trial of nitrogen mustard in 41 patients with bronchogenic car-
cinoma of the lung—one of the first large series of single agents used in solid tumors.\textsuperscript{75} He spent a year at McGill before being recruited to Toronto in 1947 as the first executive director of the Canadian Cancer Society and the newly established NCIC. Desirous of maintaining his clinical skills, he worked at Toronto General Hospital. Eventually he was asked to head up the first Canadian program for chemotherapy trials at the Princess Margaret Hospital (opened in May 1958). At the time, cancer chemotherapy was new and consisted of only a few drugs: alkylating agents, including nitrogen mustard, and the folic acid antagonists. Most cancer care was predicated on the radiation therapy model. The chemotherapy ward was to study new drugs for possible effectiveness and more probable side effects. Incidentally, it provided hope to the terminally ill.

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<td>Hodes</td>
<td>32 (20 old pts)</td>
<td>?</td>
<td>14 Jan 60</td>
<td>Aug 60</td>
</tr>
<tr>
<td>Hertz</td>
<td>8 (old pts)</td>
<td>?</td>
<td>Jun 60</td>
<td>HHCC 61\textsuperscript{c}</td>
</tr>
<tr>
<td>Warwick</td>
<td>24 (new pts)</td>
<td>Jan 60</td>
<td>Jun 60</td>
<td>HHCC 61</td>
</tr>
<tr>
<td>Hodes</td>
<td>13 (new pts)</td>
<td>Jun 60</td>
<td>HHCC 61</td>
<td></td>
</tr>
<tr>
<td>Hertz</td>
<td>14 (8 old pts; 6 new)</td>
<td>?</td>
<td>?</td>
<td>Apr 61</td>
</tr>
<tr>
<td>Warwick</td>
<td>120 (46 old pts)</td>
<td>May 59</td>
<td>?</td>
<td>Sep 61</td>
</tr>
<tr>
<td>Whitelaw</td>
<td>55</td>
<td>Jun 60</td>
<td>?</td>
<td>Sep 61</td>
</tr>
</tbody>
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\textsuperscript{a} 8 pts total 26 courses. longest remission 5 mos  
\textsuperscript{b} 8 pts total 26 courses. most 6 courses. longest remission 6 mos  
\textsuperscript{c} 8 pts total 26 courses. most 6 courses. longest remission 6 mos  

Dr. Warwick recalls that Noble and Beer came to Toronto, somewhat mysteriously without an appointment, bearing dark brown ampoules of purified vincleukoblastine and explaining what little they had been able to determine of its mode of action.\textsuperscript{76} Warwick was already well-acquainted with Noble for his contributions to the research advisory board of the NCIC. He understood that Noble had tried to interest clinicians in London, Ontario without success. To this day, he marvels that the dose that they selected to use in humans, based on their experience with rats, continues to be the dose used today.\textsuperscript{77} Warwick also remembers that the first patient to whom he gave VLB was a 29-year-old male lawyer with Hodgkin’s disease. Before the man’s death, a marked decrease in the size of his lymph nodes was ob-
Poisoning the Spindle

served, but the drug had to be stopped because of gastrointestinal bleeding; the case was counted a treatment failure with drug side effects. In retrospect it was neither.

Warwick slowly began to accumulate the first large clinical series with VLB as a single agent. His early report noted "mental changes" or "effects on the nervous system," but he still berates himself for failing to document the neurotoxicity of the drug in absent deep tendon reflexes. It would have appeared, he said, "if we had done the examination."

The head nurse on Warwick's Metabolic Research Ward from 1958 to 1961 was Rosemary Grant. Fresh out of her training at Wellesley Hospital, she witnessed the desperation and gloom surrounding the admission of patients to the small service of 10 private rooms on the fifth floor. These people were expected to die, she explained, "at the end of the line." Even those who actually responded to the drugs would die sooner rather than later; the drugs were being tested in them "instead of the animals." In fact, she told me, the animal laboratories were just a little further down the same corridor. The nurses were to offer comfort and "monitor changes." "Chemotherapy was such a new thing" that no protocols had been established; we were "just groping," she said. We did a "heck of a lot of blood work" and were "really tuned in," making observations, and prepared to "report the least thing." The only way to cope with the sadness was to aim simply for the patients' comfort, to help them die with dignity. The patients were "incredible," she recalls; "they really felt you were trying to help them" and "their confidence was rewarding"; it kept you going.

Nurse Grant cannot remember the details of Vinca testing—all the drugs had numbers instead of names—but she does remember something special happened that year, because for once one of the drugs seemed to work, sometimes. "It was quite a dramatic response" with "few side effects" and "people were quite excited."

Warwick's resident, the future distinguished oncologist Dr. Ruth Alison, has similar memories. The VLB research was already underway when she joined the team, but she was a co-author on the final paper that reported on 120 patients. Of the 27 patients with Hodgkin's disease in the series, more than half (14) had responded to VLB. The experience of collecting so many cases as evidence made a strong impression on her. At the oncology meetings in 1960, she was disturbed by reports of small samples of 20 patients or fewer. With nurse Grant, she remembers the excitement—"Canadian excitement"—about involvement in a carefully conducted study on a promising new drug in the very early days of cancer chemotherapy on the investigative ward of the fledgling hospital.

Although Noble repeatedly told Warwick that he was the first to perform clinical tests, Warwick himself suspected that the Americans had
used the drug in humans first.\textsuperscript{86} Dr. M. E. Hodes of Indianapolis certainly could stake a claim to priority: his abstract on experience with 20 patients was printed in November 1959.\textsuperscript{87} Hodes remembers that “Lilly wasn’t happy with my results (Leuroside I believe). The stuff I was given was, as I recall, very toxic.”\textsuperscript{88} Similarly Dr. Roy Hertz of Washington could stake a claim for priority. He had already led chemotherapeutic trials with other drugs on choriocarcinoma,\textsuperscript{89} and quickly treated eight women with VLB for choriocarcinoma; five of the eight responded. Hertz reported on this same experience at several meetings and he tested the Vinca drugs on choriocarcinoma maintained in an animal host. On at least one occasion he thanked Hodes for advice based on his “earlier” experience.\textsuperscript{90}

In 1999, when I asked them, neither Hertz nor Hodes would claim priority; they remember only the pleasant collaboration with the Canadians and Lilly’s support. Both clinicians were already engaged in large programs to provide clinical testing of other cancer drugs—VLB was just another agent. Hertz described J. S. Johnson as a “most cooperative Director of research.”\textsuperscript{91} Hodes wrote that the Lilly “people I dealt with admired Noble’s observation (leukopenia after administration of an antidiabetic potion) and its follow-up. “First rights” or right of first publication, at least at the clinical level, were a precious commodity—a commodity that commanded respect. Hodes recalls that chemotherapy was in such disrepute that colleagues teasingly referred to VLB as “Krebiozen,” linking it to a widely publicized and eventually discredited cancer “cure” that first captured public imagination in 1951 and continued to evoke polemic as late as 1963.\textsuperscript{92}

All the researchers I have interviewed emphasize that the Vinca alkaloids were promising because they represented an entirely new class of drugs with a new mode of action. The ability to combine drugs with differing toxicities against the same tumor target was the eventual making of combination chemotherapy as a powerful treatment choice.\textsuperscript{93} These days of new successes were heady indeed. Hodes recalled, “My friend Elliott Osserman wasn’t too happy with me when I presented data at Columbia over an hour late, because we were held up by questions during presentation of the same data at Sloan Kettering Institute.”\textsuperscript{94} When asked what he recalled of the early trials, Hodes replied: “the remarkable thing about the drug was that it worked.”\textsuperscript{95}

Hodes mentioned the “Hertz-Hodes race” and wondered if Hertz had been brought into the trials early because of his friendship with Gordon Svoboda.\textsuperscript{96} But Hertz himself—now 90 years old—credits Bob Noble for sending him “a generous sample of the extract.”\textsuperscript{97} The two men knew each other from meetings and they shared an interest in hormones and cancer.\textsuperscript{98} Hertz eventually claimed that these single drug tri-
als were useful more for delineating the side effects than they were for provoking cures.¹⁰⁰

Did Noble actually have enough of his precious commodity to give some away to an American scientist so early in his work? Clearly he was frustrated with local clinicians for not accepting the challenge. Princess Margaret Hospital had only just opened its doors and Warwick seemed stubbornly bent on collecting large numbers of patients before pronouncing on the drug.¹⁰¹ Hertz was already set up for clinical testing and understood the relationship of hormones to malignancy. Noble seems to have forgotten that he had involved Hertz so early in the research. Indeed, the printed record is obscure. In their publications, both Hertz and Hodes thank Lilly for providing VLB, and both began their clinical trials in humans before Beer’s method appeared in print and less than a year after it was announced.

Almost simultaneously in January 1960, the Canadian and American teams submitted five different articles about Vinca clinical testing to the leading journal Cancer Research; they were published in the August issue.¹⁰² By June 1960, a conference was held at Honey Harbour in Georgian Bay. Noble, Beer, Cutts, Warwick, Hodes, Hertz, Whitelaw, and Johnson of Lilly, all attended to communicate the results of their chemical and clinical testing. Noble gave the introduction.¹⁰³ Hodes and Warwick both reported on new experience with new patients; Hertz reported again on his original cases; Beer presented the results of his studies on the metabolism of the drug, and Cutts gave evidence of its anatomical toxicity. Unfortunately no one appears to have taken (or kept) any photographs.

On 3 March 1961, at around 2 p.m., Eli Lilly Co. announced the commercial availability of a new anti-cancer agent, vincaleukoblastine, which they called Velbe. This news had been heralded by a mysterious jump in Lilly stock of 12 points over the preceding week and another five points on the morning of the announcement. The financial mystery was dispelled only to be replaced with a potential crisis when an anonymous cancer researcher was quoted in the New York Times as having said that his test results were “not of sufficient moment to encourage the pursuit of further work.”¹⁰⁴ Three months later, the economic costs of grants and benefits for cancer treatment were the subject of another report in Toronto’s Financial Post. In that article, VLB was described as a plant chemical “developed” at London, Ontario.¹⁰⁵

From a commercial as well as a clinical perspective, VLB was just the beginning. According to Johnson, only three alkaloids of the more than 60 isolated from periwinkle made it to human trials;¹⁰⁶ the most active alkaloid of all was never developed because it was found in amounts too small.¹⁰⁷ Using their impressive methods, Lilly later went on to isolate the drug vincristine, another periwinkle alkaloid found in even
smaller quantities. More potent, with an unusual neurological toxicity, and owned completely by industry, vincristine always attracted more media attention than did VLB. As soon as the first clinical trials with vincristine were announced by Hodes's team at an Atlantic City meeting in April 1962, the new Eli Lilly product received media attention, in which it was compared favorably to “ineffective” VLB, despite the great similarity of their chemical structures. Almost in retaliation just two months later, Noble’s team at Vancouver used the excuse of a visit by Charles Dodds of the Courtauld Institute to feature their own discovery of VLB and its antileukemia potential in the financial press.

Vincristine, together with other agents, enabled the Boston team of Emil Frei III to announce an effective treatment for childhood leukemia in 1962. It was released for the treatment of childhood leukemia in July 1963, and it was the subject of numerous international conferences. Almost 40 years later, it still is the mainstay of remission induction in childhood leukemia.

In 1985, vincristine brought Lilly’s research director Johnson the prestigious Bruce F. Cain Memorial Award for Cancer Research—a prize he was awarded jointly with Robert Noble for the discovery of vinblastine. The title that Johnson used for his Cain lecture picked up on Noble’s theme of “chance” and indicated his opinion of the favorable contribution of industry in pharmaceutical research: “Rational Drug Screening: Serendipity to Selectivity.” He opened with these words: “The Vinca alkaloids were discovered independently in two separate laboratories by a combination of serendipity and what I have called rational broad spectrum tumour screening.”

If the discovery of the anti-tumor properties and the isolation of the alkaloid responsible had been a complex process involving several teams in several places, demonstration of its beneficial effects on living patients with malignancies was the object of many more teams in more places—a race for priority. Yet I must admit that my impression that there was a priority race is based on the tracks left in publications and in opposition to the recollections of the researchers themselves.

MASTER NARRATIVE REVISITED: #3 SEGUÉ TO MICROTUBULES AND THE “NEW CLASS” OF DRUGS

VLB had been crystallized and used in humans, but its mechanism of action was still unclear. Who first noticed that it “poisoned the spindle”? That suggestion was first made, in print at least, by Johnson’s team at Eli Lilly in a paper that was submitted for publication on 7 January 1960. Cutts came to a similar conclusion in a paper submitted six months later, because he found an excess of mitotic figures (cells in metaphase) in the bone marrows of treated normal rats and mice with
But these microscopic observations did not explain how exactly the drug was able to arrest mitosis. A key concept was still missing: the tubulin protein of the mitotic spindle had yet to be described. In other words, to complete "discovery" of periwinkle derivatives as a new class of chemotherapeutic agents yet another discovery was needed. The advent of the Vinca alkaloids stimulated researchers to complete that discovery by the mid 1960s.

Even as scientists studied the effects of periwinkle, one spindle poison had already been well-known and well-used. Its "discovery" shares many features with that of Vinca: great men, forgotten heroes, priority questions, independent discoveries, technological imperatives, and a protracted history.

Colchicine—a substance derived from the autumn crocus—had been used in medicine since antiquity and figured in the work of Dioscorides. Its popularity increased in the eighteenth century when Anton von Storck recommended it as a specific treatment for gout, a role it continues to play on occasion. It was crystallized in 1884. But colchicine is strongly toxic to the gut and can cause severe nausea, diarrhea, and pain. In 1889, while studying the intestinal lesions induced by colchicine, the Sicilian pathologist Biaggio Pernice noticed a high proportion of mitotic figures in the damaged gut tissue. His work was promptly forgotten. Fifty years later, however, the property of colchicine to arrest cell division was widely used by scientists interested in chromosomes and karyotypes—whether or not they had heard of Pernice.

In 1938, colchicine's spindle-poison effect was labelled "stathmicinèse" by Brussels pathologist Albert Pierre Dustin. A decade later, Dustin's son ran across Pernice's reference and awarded him priority retrospectively. By 1960, when VLB came on the scene, colchicine was an established tool in the work of cell biologists—but how exactly it poisoned the spindle was still unknown. The technological advantages provided by radioisotopes sharpened the focus slightly.

For more than a century, light microscopists had reported seeing delicate filaments in dividing cells; by the early 1960s electron microscopists had given these filaments a name ("microtubules"), dimensions (100 to 120Å), and a location not only in the mitotic spindle—where they were found in greatest abundance—but also in the dendrites of neurons. While Beer applied tritiated-VLB to studies of VLB metabolism, Edwin Taylor was applying tritiated colchicine to a study of its mechanism of action and in 1965 he confirmed the existence of microtubules, made of the substance later named "tubulin." Microtubules became a mini-industry in cell biology and they offered a neat explanation as to why the periwinkle drugs were toxic to nerves.
as well as to rapidly dividing cells. Inevitably the extracts of periwinkle and crocus were compared.

Could a discovery of a drug be complete without elucidation of its mode of action? As noted above, the researchers involved in this discovery claimed to be excited by the recognition that the Vinca alkaloids represented an entirely "new class" of drugs with differing mechanisms of action, and differing side effects. Yet Vinca's mode of action was unknown even as it was being tested in humans. Its "new class" status as a spindle poison was only conjecture—conjecture that was not to be settled until 1965, when the pressure brought by the discovery of the Vinca alkaloids brought to completion yet another discovery in cell biology: that of the spindle itself.

MASTER NARRATIVE REVISITED: #4 BACK TO VINCA

These amplifications to the story still leave us with a number of questions. When exactly did Noble first begin looking at the leaves? For how long did the London team try to grow and manufacture enough drug for testing? Who was Miss Farquharson? And above all how did an endocrine team actually think to look at the drug as a potential cancer agent rather than as a weak source of hormone too toxic to investigate? After all, nothing in the original protocol should have induced them to measure white blood cells in rats: the technique was cumbersome, time-consuming, and costly. Following yet another speech on his discovery, the aging Noble was asked, "Why ever did you look at the white cells in the first place?" He replied that in all honesty, he did not know.

Seated in the audience for that speech was someone who did know the answer to the question, but did not have the nerve to speak up. Polish-born Halina Czajkowski Robinson (b. 1927) had survived the camps of Auschwitz and Bergen Belsen and been relocated by the United Nations and the Red Cross to Sweden in 1945 where she entered university to study chemical engineering. She graduated with high marks earning herself a place in the Karolinska cancer research laboratory of George and Eva Klein. Although her background was in applied basic science, she mastered a number of delicate biological techniques, including the determination of blood sugar and of white cell levels. At the outbreak of the Korean war, many refugees sought to move again and Halina with her parents (her father had been found after the war) was relocated to Canada. She hoped to return to engineering and was advised to choose London because it was "central." With irony, Halina told me how she quickly learned that the London, Ontario of 1951 was not yet ready for a woman engineer. In May 1951, J. B. Collip gave her work in his laboratory on the strength of her experience with the Kleins at the Karolinska. Her supervisor was Robert Noble (Figure 2).
As soon as Halina arrived, Noble showed her periwinkle leaves in a box and explained that the team was looking for an effect on blood sugar levels. She was to measure glucose in the blood of rats given oral extracts. But she did not want to lose the other skills that she had so recently acquired in Sweden. As a result, she performed blood cell counts too. When the experiments turned to injections on or before 8 September 1952, she observed the decline in white cell counts. At first she thought it was an error, but the finding occurred on repetition, and she accumulated and confirmed her results, during the year of 1953. Finally she showed her results to Noble. He listened to her politely without saying much, and then he sent samples out to the hospital laboratory for confirmation. She was not offended—she respected his desire for accuracy and she thought that his listening to her at all was a mark of tolerance. Parallel work on autopsies and comparisons with the effects of cortisone given to animals was carried out.\textsuperscript{125}

Figure 2

Halina Czajkowski (later Robinson) circa 1951, photograph provided by Halina Robinson.
Dr. Vernon Colpitts, cited by Noble as the one who observed the crucial drop in the white cell count, was not involved with the periwinkle project at all; he had been working on estrogenic effects found in extracts of a different plant, Lithosperm. Halina recommended that the team perform chromatography to isolate the active component, but that technique was not applied until the arrival of Charles Beer in 1954. Halina left Noble’s lab in October 1955 to direct the Pediatric Research Laboratories of War Memorial Children’s Hospital in London, Ontario, where she remained until her retirement in 1976. She gave her notebook to Collip, but years later, it could not be found.\(^{126}\) Misspelling her name as “Helena,” Noble thanked her for her assistance in the acknowledgments of his 1958 paper.

Encouraged by Colpitts and the late Dr. Ken Carroll, Mrs. Robinson set the record straight in 1991 by publishing what she called an “anecdote” containing some of the foregoing story in the same journal that had printed Noble’s own account the previous year.\(^ {127}\) Also choosing the frame of chance—“another happenstance”—she explained that her anecdote provided one more reason why “priority for this discovery remained in Canada.” Her own white cell findings she called “fortuitous.” Noble seems to have forgotten Halina Robinson, just as he forgot Hertz. When I asked her if it might be because she was a laboratory technologist and a female—she hesitated at first—and then laughed saying, “I wouldn’t be surprised. I wouldn’t be surprised.”\(^ {128}\)

CONCLUSION

Noble and Beer moved to Vancouver in 1960 shortly after the Honey Harbour Conference. They continued to work on the chemistry, uses, and effects of Vinca alkaloids but both turned to other projects. Archivists at the University of Western Ontario are unable to trace any record or profits of the vincleukoblastine patent and neither they nor their colleagues at the University of British Columbia can locate Noble’s papers or laboratory notebooks. Lilly claims that it took many years to recover its investment, because the drugs were given away or sold at cost for a long time in an effort to keep prices down.\(^ {129}\) One of the early leukemia investigators has written that clinicians associated with U.S. National Cancer Institute went in person to appeal to the “Lilly board to produce the drug for humanitarian reasons—the lives of these little children were at stake.”\(^ {130}\) Lilly archives will not disclose what profits have been made on the Vinca alkaloids or even what quantities were sold. Warwick (who signed the royalty cheques for Noble) told Roland that profits were in the order of a hundred million dollars a year.\(^ {131}\)

At the Canadian Medical Hall of Fame, one can read how “Dr. Noble made his discovery of ‘vinblastine,’ the first major advance in chemoth-
Poisoning the Spindle

therapy originating in Canada.” You will find the master narrative, including “serendipity,” “diabetes,” brother Clark, and periwinkle leaves originating in 1952. And you will read that “working with the Eli Lilly Co., a small supply of vinblastine was prepared for clinical trials the first of which occurred in 1959 at the Princess Margaret Hospital in Toronto with very dramatic results.”132 Based on the foregoing, it seems that most of these claims are half-truths, or wrong.

Noble and Beer may have found their places in the Canadian Medical Hall of Fame, but this version of their achievement is world famous only in Canada. Lilly executive I. S. Johnson knew the team well, had been to the Honey Harbour conference and to UWO, and had even been offered a job at Vancouver by Robert Noble.133 Yet in 1992, Johnson seemed to overlook Canadian “priority” in the development of these drugs when he wrote (quite truthfully) in Science magazine 1992 that he was “the leader of the group that detected the anti-tumour activity from the plant at Lilly.”134 He acknowledged that “two different groups” had been working on the plant. To me, he wrote that “this was a classical case of two groups making similar observations, completely independently of each other.”135 As we have seen, a printed record does not prove priority.136

Indeed, it is difficult to ascertain what credit for this “discovery” should be Canadian at all. Researchers in Australia had published on Vinca’s lack of effectiveness in diabetes back in the 1920s—was it chance that Noble was still pursuing the possibility, or simply ignorance? Scientists of the pre-Medline world might be forgiven for not having noticed much earlier papers in foreign journals.

As for the cancer connection, Lilly scientists were well launched on Vinca alkaloids in cancer chemotherapy screening, and they had already demonstrated an anti-tumor effect before any Canadian applied it to the hematologic malignancies for which it is now principally used. As much as the academic team in Ontario tried to maintain respectable production, they too came to rely on the products and generosity of industry for their work.

And if priority is somewhat fuzzy, what is left for chance? Noble’s claim that cancer was “far from our minds” cannot be sustained. Before 1958, he was first or second author on no less than 13 papers on cancer research; he enjoyed NCIC funding, had a collegial relationship with Hertz based on their interest in hormones in oncology, and was regarded as an expert in tumor growth. He held priority for the important discovery of the effects of hormone withdrawal in neoplasms—the reason why Chester Stock had invited him to the New York symposium on cancer treatment in the first place. In addition, Noble had been deeply involved in finding a way to foster communication between Canadian
researchers studying cancer. As a member of the Research Advisory Group to the NCIC, he was a founder of the biennial Honey Harbour Conferences on cancer research—conferences which began in 1954—in the midst of his periwinkle studies. Furthermore, by his own testimony to Charles Roland, Noble's original goal (thwarted by Macleod) was cancer research. And in 1960—right after the Honey Harbour conference—Noble left for Vancouver to direct the Cancer Research Centre. From the beginning to the end of his career, Noble had cancer squarely in his sights. There was scarcely a time when he was not "thinking of cancer."

Noble's deep immersion in cancer research was shared by his team. With his Oxford PhD in chemistry, Beer was familiar with the latest isolation techniques and had spent three years at the Sloan-Kettering Institute for cancer research in New York City. Halina Robinson had just left a cancer research laboratory at the Karolinska Institute in Sweden where she had learned white cell counting for the purposes of assessing chemotherapy drugs—the technique she later applied in London, Ontario without Noble's direction or knowledge.

At the beginning of this paper I alluded to Noble's connection to the insulin discovery and to his partisan view of the rivalry. As a child and again after he became an adult, that story was never far from the surface—whether he was in Aberdeen, dining with the Macleods, or in Montreal and London, working with his greatly admired mentor, Collip, ever distressed over his own lack of recognition. With the unhappy legacy of insulin as a touchstone, laboratory-chief Noble seems to have played a more successful Macleod to Beer's Collip. In this country at least, his version of the story "won"—flaws and all.

I think that Noble's invocation of chance may have helped in that victory. In framing his "discovery," he could turn to "chance" because the leaves had come to him with a diabetes label affixed. On several occasions, however, he later admitted that he'd done so "tongue in cheek," because of a more serious matter about the philosophy of the research enterprise. He told Charles Roland it was to "pull the leg" of the large pharmaceutical companies and their massive screening programs that could intimidate researchers at smaller places.

At that time, the United States had a tremendous budget for chemotherapeutic drugs, and this meeting... at the New York Academy of Science... was devoted to discussing the methods of applying this. What tumors should be used and how much money was being spent? At that time they were screening virtually everything. They'd take... thousands of chemicals and, just purely at random, to see if they could pick up anything. With my tongue in my cheek, I said this [i.e. his] was a serendipitous approach, rather than this enormous vast budget which was being spent [on the principle that] something might turn up sometime. I was sort of pulling their leg a bit. Turned out to be true.
Poisoning the Spindle

After that they started to screen plants, I might say. But they just stopped just the other day... They all thought that the plant kingdom was full of things. This was too bad, that the first one was active. They haven't found one ever since. Depends on how you look at it.140

Noble seems to have been nostalgic for a different kind of science, one that he knew was on the verge of disappearing only to be replaced by something bigger, more technical, more crass, and perhaps less pure.141 To Dr. Roland, he said:

Beer and I went to Lilly's... and saw what they were doing, and they came up to Western, and it was quite obvious that we couldn't compete with their chemistry department, which was an enormous set-up, so we decided to work in collaboration with them. Eli Lilly—it was somewhat like the insulin situation.142

Beer shared Noble's research philosophy when he contrasted the Canadian team's approach with that of the pharmaceutical company. True, he may have been making a virtue of fiscal necessity, when he said:

The Lilly approach was somewhat different from ours... We would do a quite elaborate chemical fractionation and then we would test the fractions at that point by injecting them into experimental animals, into rats and, in our case, monitoring the white count. We didn't need a pure compound to do that. That was our back-up. The thread that led us through the jungle, as it were.

But the Eli Lilly Company... would probably have enough to isolate, pure, these compounds... We were on a very narrow track. We had a light we thought we saw at the end of the tunnel and we kept our eye on that biological activity. That was our approach. It was the only approach we could have done, but it worked. It probably kept us ahead. We were single-minded, not because we were more pure-minded, but because we had really no option.143

In a sense, the Canadian researchers accepted the "rules" of scientific competition: to work autonomously, they must "compete"; since the competition could not be won, they allowed Lilly to become their "patron."144 Emphasis on "chance" allowed the smaller group to be equal players and to retain their priority: "Aw shucks! We were just lucky," it modestly seemed to imply. Contributions of Vinca derivatives were often described as "gifts."145 The patronage relationship was beneficial to both sides, but the academics worried that it came at what they viewed as a philosophical cost.

Canadians have an uneasy relationship with fame, priority and money. Like any good scientist, Noble was attuned to the tremendous importance of priority—not only for fame, but also for continued funding of research in Canada. His preoccupation with the opportunities for national science in Canada was shared by the clinicians Whitelaw and Warwick who, with Noble, tended to feature the Canadian aspects of
the discovery in the opening lines of their early publications. In his conversations with Dr. Roland, Noble referred not only to the priority matters related to periwinkle but also to the priority he could claim for his other work. For example, he spoke with regret about the lack of public recognition for the role of the Noble-Collip drum in the "discovery of chlorpromazine" credited to Poullenc Frères.

By 1988, Noble was 78 years old and still actively engaged in research. Harold Warwick thought that he was "bitter"—over loss of NCI support late in his career, and perhaps over not receiving enough credit for Vinca drugs and his later work on tumors. Again drawing a parallel to insulin, Warwick told Charles Roland,

He's not winding down graciously. I wish for his sake... he'd say "I've had my day"... He's an angry older man... I have a feeling that Beer and Cutts had been left just a little in the background... that they haven't received the recognition they might have... I've had the feeling that the fellow who really, night after night, was working there and actually produced the crystalline substance... that was a pretty important thing—just as important as Dr. Collip.

Beer took a different, more sympathetic view. Attached to the Vinca research and admiring of Noble's qualities, Beer contentedly followed his boss to Vancouver. He found Noble not only "pleasant" and "affable," but also "stimulating" and "imaginative,"

full of ideas... always watching for something which is a little out of the ordinary and then he'll push it. He may push it a little further than a cautious person would, which is a good thing, but he's quite ready to pull back and change... He's deserved the honours that he's got. I think in some cases he's been slow in getting them.

Noble had wanted to publish his 1984 Terry Fox lecture amplifying on the discovery, but had difficulty finding a place for it. He tried the medical student journal at Western, but "the dean wasn't very keen on it." A version of the lecture was read again in 1989 and finally published the following year—in the month of his death.

Like a good historian, Noble strove for evidence, accuracy, and care in all his endeavors, including the story he told of the discovery. His periwinkle tale might seem to have lacunae to us now, but it contained the features that mattered to him. He packaged it in a "diabetes/chance" wrapper because that is how periwinkle first captured his attention. But it is clear that in looking for A (a source of insulin), Noble himself and his team were already deeply immersed in a search for B (cancer cures). Their minds were far more than prepared.

Noble's perspective has much to tell us. When we historians put together a story, we use the sources that are available and decide how much we can trust them. Noble's accounts are out there in cold hard
print, but his papers cannot be traced and many of the players are now dead. The Lilly company will not let me into their records, Halina Robinson's notebook is lost, Noble and Johnston family descendants cannot trace personal papers, and I'm still looking for Miss Farquharson. To the extent that these accounts can be reconciled, I have relied on what people recollected for me or for Charles Roland. But memory is a funny thing. Events fall into structural sequences that seem logical in retrospect and national and personal egos enter into play. In addition to whatever personal reasons Noble may have had for wanting to emphasize his priority, he also had a long-standing commitment to the status of research in this country, and—as Alison Li and Terrie Romano have shown—an important discovery was the best of all possible ways to validate continued support. Doubly conflicted both by the pressure of the reward system in science that demands originality, and by a national characteristic that values modesty, Noble found that invoking chance as a fellow actor in his discovery allowed him to retain humility, even as he staked his claim to priority in the face of American big business.

To conclude, I doubt that the physiological process of any discovery can be reconstructed because of the nature of our sources and the traditions of preservation. In the case of the Vinca alkaloids, I think that the discovery was not solely Canadian but a multiple discovery that took place in at least two different laboratories and involved the crucial observations of many more people than Noble's master narrative was able to recall. Furthermore, the discovery took place at no particular moment because it involved a series of iterative steps, from recognition of activity, to isolation, purification, clinical testing and manufacture—all of which were essential for the production of the new cancer drugs. Notwithstanding the protests of the players, a priority race for isolation, clinical testing, and the demonstration of positive results did indeed ensue. In fact, the hesitation of the main actors to label it a "race" is a testimony to the ambiance of collegiality and personal good will that they managed to establish within the confines of their scientific endeavors.

Finally, I remain squarely in the camp that is suspicious of the role ascribed to chance in this or any other discovery. Notwithstanding the title of that seminal paper of 1958, chance was not a big factor after all. Or, let us say chance plays a role in every discovery—in the guise of "experience (or experiment)" that brings an event to the observation of an informed mind. In that sense, its part is banal.

One thing is clear, however: Charles T. Beer devised a method for isolating vincleukoblastine—the first of the effective Vinca alkaloids—but only vincleukoblastine. The isolation and development of the 60 other alkaloids and the more frequently used drug, vincristine, belongs
entirely to the Eli Lilly company. "Were there celebrations?" Chuck Roland asked Beer back in 1987. "No not particularly" came the reply. "My main feeling was one of relief. "Thank God that's over,"" Beer said.155

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I am especially grateful to the many people contacted during this project, all of whom responded to my questions with enthusiasm. They are Dr. Charles Beer, Dr. Donald Christian, Alison Li, Halina Robinson, Dr. O. Harold Warwick, Dr. Ruth Alison, Rosemary Grant, Dr. M. E. Hodes, Dr. Roy Hertz, Dr. Irving S. Johnson, Dr. Charles G. Roland, Mrs. Mary Heighington, the vast, interconnected Farquharson clan, and the descendants of Dr. and Mrs. C. D. Johnston in Jamaica and Canada. I thank Adrian F. ailson, Robert David Wolfe, Cherrilyn Yalin, and an anonymous reader for comments on earlier versions of this paper.

NOTES


5 In an effort to locate consensus on individual discoverers, Lindahl et al. have suggested the use of citation indices. Admitting that discoveries can be multiple yet with an inexplicable deference to the "need" to find the firsts (e.g., the Nobel prize or the Lasker prize), they contend that citation patterns reflect the consensus of the scientific community. Using the discovery of HIV and citation practices as an example, they awarded priority to the team of Montagnier at the Pasteur Institute. It remains for someone to find an example of erroneous consensus. B. I. B. Lindahl, Aant Elzinga and Alfred Welljams-Dorof, "Credit for Discoveries: Citation Data as a Basis for History of Science Analyses," Theoretical Medicine, 19 (1998): 609-20.

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tion," "method," "practice," "relativism," and "realism" are far more numerous than the entries on "discovery," "chance," or "accident."


15 In a speech read at Lille in 1854, Louis Pasteur is said to have remarked: "in the fields of observation, chance favors only the mind that is prepared." René Vallery-Radot, Life of Pasteur, translated by R. I. Devonshire, (Garden City: Garden City Publishing, 1927), p. 76. On uses of this famous quote, see for example, Comroe, "Roast Pig and Scientific Discovery," p. 854; Rossman, "Serendipity in Medical Discovery" (1965); Dillip V. Jeste, J. Cristian Brannigan, Social Psychiatry-A Myth? Archives of General Psychiatry, 36 (1979): 1173-78; and Peter Medawar, "Can Scientific Discovery be Premeditated?" in Peter Medawar, The Limits of Science, (New York: Harper and Row, 1984), p. 45-54.


17 Kantorovich, Scientific Discovery; Jeste et al. "Serendipity in Biological Psychiatry"; Comroe, 'Roast Pig and Scientific Discovery Part II,' p. 1035-44.

18 For example, Jeste et al. "Serendipity in Biological Psychiatry."

19 Brannigan, Social Basis of Scientific Discoveries, p. 11.


22 One notable exception is John Patrick Swann, Academic Scientists and the Pharmaceutical Industry: Cooperative Research in the Twentieth Century (Baltimore: Johns Hopkins University Press, 1986).

23 For example, Gerhard Domagk who worked for Bayer and won the 1939 Nobel prize for the first sulfa drug; Gertrude Elion and George Hitchings of Burroughs Wellcome who shared the 1988 Nobel prize with James Black of SmithKline and French, for their multiple discoveries of "rational derivatives."

24 Robert L. Noble, Interview with Charles G. Roland, 31 January 1986, "Experiences in Research, Particularly with Respect to Vinblastine, 1950s," HCM 2-86, p. 2. Noble continued "Macleod was just the opposite that everything and everybody's written about him, except Michael Bliss" (p. 4). The coin toss had first been reported by Banting. Citing both Best and Noble, Stevenson suggested that the toss never happened. Lloyd G. Stevenson, Sir Frederick Banting (London: Heinemann Medical Books, 1946, 1947), p. 78, 79n. Bliss described it twice: in 1982, he wrote that no evidence supported the legend that Best had "lost"; in 1984 he wrote, "Best won"—which is certainly true from the sense of posterity. Michael Bliss, The Discovery of Insulin (Toronto: McClelland and Stewart, 1982), p. 57-58; and Michael Bliss, Banting. A Biography (Toronto: McClelland and Stewart, 1984), p. 59.

25 "It's intriguing for me to hear about the pre-insulin days. The family was sort of bound up by it, so I've been hearing about it since I was a little boy." Robert L. Noble, in his Interview of Walter Campbell, undated ca. 1970, p. 10. "[Charles Best] and my brother worked out of Georgetown where they were students... and Charly and Margaret were engaged, and I used to know them as a small boy. I've known them for many, many years. They've changed considerably." Robert L. Noble in his interview of Harold Ettinger, undated ca. 1970, p. 14. When Ettinger opined that the "great advertisement of Charly is by his wife rather than by Charly," Noble replied

26 "At that time, I'd read somewhere or other that [Lumsden] . . . at Guy's Hospital published that he was curing, he thought he could cure, cancer. If you took one strain of tumour, one strain of rat or mouse [tumour] and transplanted it into another, it would be rejected. This, not knowing anything about it, excited me and I wrote Professor Macleod, and Macleod's letter was very guarded. I didn't know what he thought of Lumsden. Anyway I didn't go to Lumsden." Robert L. Noble, Interview with C. G. Roland, 31 January 1986, p. 5. Macleod may well have had an opinion of Thomas Lumsden, since the latter's degree was from Aberdeen according to his_Lancet_publication. The articles Noble had seen seem to be the following, although the work originated from London Hospital not Guy's: T. Lumsden, T. Macrae and E. Skipper, "A Note on Certain Effects of Tumour-Immune Rat Sera Revealed by Cinematography," _Journal of Pathology and Bacteriology_, 40 (1935): 418-19; Thomas Lumsden, T. F. Macrae, and Eric Skipper, "The Direct Demonstration of Anti-Cancer Bodies in the Serum of Animals Immune to a Homologous Tumour," _Journal of Pathology and Bacteriology_, 39 (1934): 595-607; and T. Lumsden, T. Macrae and E. Skipper, "The Mechanism of Homologous Tumour Immunity," _Lancet_, 1 (1934): 731-32.


35 In particular, Cutts was to read a version of the paper in April 1958 in Philadelphia and the _Toronto Telegram_ of 12 April 1958 indicated that the team was on the verge of finding a cancer cure. "Well Cutts was nervous anyway and he saw this and he had a fit." Robert Laing Noble, Interview with Charles G. Roland, 1 February 1986, "Experiences in Research, Particularly with Respect to Vinblastine, 1950s," HCM 2, 86, p. 32-33.


37 Noble, "Discovery of the Vinca Alkaloids" (1990), p. 1345.

38 C. D. Johnston, Medical Faculty, _McGill University Yearbook_, 1914. McGill University Archives.
39 "Dr. C. D. Johnston, Physician and Dairy Farmer Dies at 83," Gleaner (Kingston, Jamaica), 16 October 1968—includes text of citation read at his retirement in 1949; and Myrnelle McIntosh [Johnston's daughter now deceased], "Nostalgia: Bush Medicine and Modern Science," Sunday Gleaner (Kingston, Jamaica), 1998; and Myrnelle McIntosh, "Nostalgia: Practising Medicine in the Early 20th Century," Sunday Gleaner (Kingston, Jamaica), 16 July 1995. These articles were kindly provided by Johnston's granddaughter, Sandy McIntosh of Kingston Jamaica, via e-mail and telephone interview, 7 October 1999. Other information came from Dr. Donald Christian of Kingston Jamaica, telephone interview, 1 October 1999.

40 Sandy McIntosh remembers her grandmother "drying masses of periwinkle plants on the back verandah of her house in Black River," personal communication, 8 October 1999. Charles Beer remembered a "small package" of a few leaves arriving "every month or so." Charles T. Beer, Interview with Charles G. Roland, "Experiences in Research, Particularly in Regard to Vincoleucoblastine [sic]," 2 February 1987, HCM 3-86, p. 16.


42 I am especially grateful to Clark Noble's daughter, Mrs. Mary Heighington, for looking into this matter for me.

43 Noble, "Discovery of the Vinca Alkaloids" (1990), p. 1348.

44 Noble, "Discovery of the Vinca Alkaloids" (1990), p. 1346.

45 Noble, "Discovery of the Vinca Alkaloids" (1990), p. 1345.


48 Beer, Interview with C. G. Roland, 2 February 1987, p. 6, 7-11.


51 Beer, Interview with C. G. Roland, 2 February 1987, p. 11.


57 Leurosine eventually became Vinleurosine. Svoboda extended his filial homage to names for other isolates, but the nomenclature committees did not retain his preferences, e.g., Vinleurosidine (Vinrosidine); Leurocristine (Vincristine).

58 The manuscript of the first report was received by the journal on 29 September 1958. Here and in several other reports, Svoboda implied that his isolation had predated that of Beer. In the first report, he stated that physical properties show the isolates to
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59 Noble, Interview with C. G. Roland, 31 January 1986, p. 35; and 1 February 1986, p. 25.


63 Noble, Interview with C. G. Roland, 31 January 1986, p. 35.


70 Noble, Interview with C. G. Roland, 1 February 1986, p. 22.

71 Noble, Interview with C. G. Roland, 1 February 1986, p. 22.

72 O. Harold Warwick, 1988, Interview by Charles G. Roland, 21 January 1988, HCM 2-88, p. 16. Unfortunately, the University of Western Ontario no longer has any record of these transactions, nor does it have a record of the income derived from the patent which expired 20 years ago. I am grateful to archivist Theresa Regnier for looking into this matter for me.


75 The results were read at the Royal Society of Medicine in 1947. O. Harold Warwick, Interview with J. Duffin, 12 September 1998.


Warwick, Interview by J. Duffin, 12 September 1998. Warwick made the same observation to C. G. Roland, Interview 21 January 1988, p. 21. Warwick may be right that he would have found the problem in his large series if had he looked; however his patients had no symptoms and his team had yet to devise protocols. Although neurotoxicity is more frequent with the later isolate, Vincristine, the American teams had documented paresthesias and the absence of deep tendon reflexes early in the VLB work. In other words, Warwick would have learned of his oversight while his research was in progress. Roy Hertz, M. B. Lipsett, and R. H., Moy, "Effect of Vincaalkoblastine on Metastatic Choriocarcinoma and Related Trophoblastic Tumors in Women," Cancer Research, 20 (1960): 1050-53.

Rosemary Grant, Interview with J. Duffin, 21 April 1999.

Rosemary Grant, Interview with J. Duffin, 21 April 1999.


Dr. Ruth Alison, Interview with J. Duffin, 13 January 1999.


M. E. Hodes, R. J. Rohn, and William Bond, "Effects of a Plant Alkaloid, Vincaalkoblastine, in Human Beings [abstract no. 67]. Proceedings of the 32nd Annual Meeting," Journal of Laboratory and Clinical Medicine, 54 (1959): 826-27. The meeting was held 5-6 November 1959. None of Hodes' early reports included dates when treatment began. I have been unable to determine the date of submission for this abstract. By the time the paper was read, Hodes' sample had grown to 32 patients, but it was not until January that analysis was available for 27 of these patients. M. E. Hodes, Robert J. Rohn, and William H. Bond, "Vincaalkoblastine. I. Preliminary Clinical Studies," Cancer Research, 20 (1960): 1041-49.

M. E. Hodes, e-mail letter to J. Duffin, 11 January 1999. The results of these clinical tests appeared in abstracts: M. E. Hodes, R. J. Rohn, W. H. Bond, and J. Yardley, "Clinical Trials with Leurosine Methidione, an Alkaloid from Vinca Rosea, Linn.," Cancer Chemotherapy Reports, 28 (1963): 53-55.


Hertz and Moy, "Therapy of Methotrexate-Resistant Choriocarcinoma"; Roy Hertz et al., "Effect of Vincaalkoblastine on Metastatic Choriocarcinoma and Related Trophoblastic Tumors," p. 1053 (thanks Hodes); Roy Hertz, J. L. Lewis and M. B. Lipsett, "Five Years Experience with Chemotherapy of Metastatic Choriocarcinoma and re-

91 Roy Hertz, letters to J. Duffin, undated (May 1999) and (29 July 1999).

92 M. E. Hodes, e-mail to J. Duffin, 12 January 1999.


94 In October 1963, the N.C.I. of the United States announced that it was seeking 40 previously untreated patients with Hodgkin’s disease of a combination chemotherapy trial in which vincristine was one of the agents. See “Hodgkin’s Disease to Get 4-Drug Test,” *New York Times*, 4 October 1963, p. 71, cols. 4-5. One month later, the public read reports of how the “combined approach” (radiotherapy and chemotherapy) had produced “cures” of mouse leukemia. “Leukemia Reported Cured in Mice Tests,” *New York Times*, 22 November 1963, p. 33, col. 7.

95 M. E. Hodes, e-mail to J. Duffin, 12 January 1999.

96 M. E. Hodes, e-mail to J. Duffin, 11 January 1999.

97 M. E. Hodes, e-mail to J. Duffin, 12 January 1999.

98 Roy Hertz, undated letter to J. Duffin, (May 1999).

99 Roy Hertz, letter to J. Duffin, 29 July 1999.


101 “He told me that he tried to interest some people here [London, ON] but he couldn’t arouse any interest.” Warwick, Interview with J. Duffin, 12 September 1998. Like Noble, Warwick was surprised that his early positive results could not interest his colleagues. He wonders if he received no reply to his letter to David Kamofsky of the Sloan Kettering Institute in New York City because of Kamofsky’s own premature and terminal illness with bronchogenic cancer. Warwick, Interview with J. Duffin, 12 September 1998.


106 One other source states that four isolates were tested clinically. William L. Laurence, “Science: Cancer Research” *New York Times*, 15 December 1963, IV, p. 7, col. 7-8. The four substances would have been Vinblastine, Vincristine, Leurosine (Vinleurosine), and Leurosidine (Vinrosidine).

107 I. S. Johnson, Interview with J. Duffin, 15 May 1999, and letter to J. Duffin, 18 May 1999. The most active drug was Vin-leurosidine.


124 From their microbiology and tumor laboratories at the Karolinska Institute, the Kleins established distinguished research careers and continue to publish in leading journals, including Cancer and Nature.


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133 I. S. Johnson and R. L. Noble got along very well. Johnson went to Vancouver to consider Noble's offer, but eventually declined because he thought his resources for research were "not as good" as those at Eli Lilly. I. S. Johnson, Interview with J. Duffin, 15 May 1999.

134 Irving S. Johnson, "Drugs from Third World Plants [letter]." Science, 257 (1992): 860. In fairness I should add that this letter was in response to an ill-informed editorial complaining that Lilly had enjoyed "easy pickings" on the Madagascar periwinkle—which actually had been grown in Jamaica, Philippines, Ontario, and Texas—"without ever paying Madagascar a dime"! Richard Stone, "The Biodiversity Treaty: Pandora's Box or Fair Deal?" Science, 256 (1992): 1624.


136 Since the conventions established by the 17th-century deliberations of the Royal Society of London, dilemmas over priority have been settled by date of publication. Due to lag time from submission to printing, leading journals have taken to indicating the date of submission and acceptance on every article. The practice itself seems to provide more evidence for the claim that discoveries are the inevitable product of zeitgeist and that chance is of little consequence. Leslie Roberts, "The Rush to Publish," Science, 251 (1991): 260-63; B. I. B. Lindahl, Aant Elzinga and Alfred Welljams-Dorof, "Credit for Discoveries: Citation Data as a Basis for History of Science Analyses," Theoretical Medicine, 19 (1998): 609-20.

137 Noble, Interview with C. G. Roland, 1 February 1986, p. 61-66. "There was a need to stimulate interest in research in Canada." On the commitment of the NCI to Canadian science and scientists, see "Dedicated Medicos," Saturday Night, 24 April 1951, p. 21.

138 "Macleod was just about the opposite that everything and everybody's written about him, except Michael Bliss. He was very gentlemanly, very quiet-mannered, a Scotchman with a very quiet sense of humour. He very seldom showed any expression of anger.... He was a very delightful person. He had a great respect for German scientists. He read German.... in all the years, after all this squabble over insulin, I never heard him say anything at all derogatory about either Best or Banting. The only thing he did say, he said, if he'd stayed in Toronto, he would have had to take Banting to court, and he didn't want to do this." Noble, Interviews with C. G. Roland, 31 January 1986, p. 6, and 1 February 1986, p. 19-20. This same view is evident in the undated interviews Noble conducted with Harold Ettinger and Walter Campbell ca. 1970 in preparation for a planned biography of Collip. In the interview with Ettinger especially, disappointment, hurt, bitterness, and jealousies felt by others come up often. I am grateful to Alison Li for providing me with copies of these fascinating documents in which the interviewer spoke as often as his subjects.


142 Noble, Interview with C. G. Roland, 1 February 1986, p. 20.


148 Noble, Interview with C. G. Roland, 31 January 1986, p. 24. He claimed that he dare not work with his own invention (the drum) again for fear of anti-vivisectionist attacks. Noble expressed the same regret in his interview of Harold Ettinger, undated (ca. 1970), p. 33-34. In the same interview, Noble said, “My better ideas in the war were all turned down by the NRC” (p. 37).


153 Alison Li and Terrie Romano, “Insulin’s Long Shadow: The Politics of Medical Research in Canada” paper read at the annual meeting of the American Association for the History of Medicine, Toronto, 1998.

154 The impact of the rise in the funding of research by pharmaceutical firms is a topic that has yet to be explored by historians of medicine.